Failure of Posaconazole Therapy in a Renal Transplant Patient with Invasive Aspergillosis Due to *Aspergillus fumigatus* with Attenuated Susceptibility to Posaconazole

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We report the case of a kidney transplant recipient with invasive aspergillosis due to *Aspergillus fumigatus* resistant to voriconazole and immediately susceptible to posaconazole who failed posaconazole therapy. Plasma posaconazole concentrations indicated an unfavorable ratio of the area under the concentration-time curve over the MIC. Posaconazole should be used with caution for invasive aspergillosis caused by strains with attenuated posaconazole susceptibility, as drug exposure may be inadequate, resulting in therapeutic failure.

Acquired azole resistance has been reported to be an emerging problem for patients with aspergillosis (3, 11, 13, 14). In resistant *Aspergillus* isolates, mutations in the *cyp51A* gene may lead to various non-wild-type susceptibility phenotypes of the licensed azole drugs (3, 12). Itraconazole commonly shows no in vitro activity, while the activities of voriconazole and posaconazole may be attenuated; i.e., the MICs are elevated compared to those of wild-type isolates, but the drugs retain moderate in vitro activity (8, 12). Here we describe the first case of an azole-naïve patient with aspergillosis due to an *Aspergillus fumigatus* isolate resistant to voriconazole and with reduced susceptibility to posaconazole, for whom posaconazole treatment failed. The measurement of posaconazole concentrations in blood indicated a probable failure to achieve the pharmacodynamic target.

A 51-year-old female kidney transplant patient, weighing 104 kg, was admitted to our hospital in October 2009 with abdominal pain, fever, leukocytosis, and increased C-reactive protein (CRP) and creatinine levels (350 μg/ml). After the MIC results became available, antifungal susceptibility testing using EUCAST methodology (6) showed that voriconazole was inactive (MIC > 16 μg/ml); MICs of itraconazole and posaconazole were 2 and 0.5 μg/ml, respectively. The amphotericin B MIC was 0.5 μg/ml. After the MIC results became available, voriconazole was replaced by posaconazole at 200 mg four times a day (q.i.d.) after a loading dose of 400 mg b.i.d. on the first day. The tacrolimus dose was reduced by 50%. Antifungal susceptibility testing using EUCAST methodology (6) showed that voriconazole was inactive (MIC > 16 μg/ml); MICs of itraconazole and posaconazole were 2 and 0.5 μg/ml, respectively. The amphotericin B MIC was 0.5 μg/ml. After the MIC results became available, voriconazole was replaced by posaconazole at 200 mg four times a day (q.i.d.), aiming at an exposure above 1 μg/ml. However, after 1 week of therapy under steady-state conditions, the trough plasma posaconazole concentration measured 0.6 μg/ml. The dosing regimen was changed to 200 mg six times daily with intake after the intake of high-fat-containing food. The increased posaconazole dose still yielded the same concentration after the second week of therapy.

During the following months she remained intermittently febrile. In November, renal biopsy specimens revealed tubulitis and interstitial inflammation. A 3-day course of methylprednisolone was given for possible transplant rejection.

In January 2010, the stenotic transplant ureter was replaced by a nontreated ureter. Preoperative urine was sterile. Perioperatively, pus and a necrotic transplant ureter were found medially to the transplant. A Blankophor stain of the purulent material showed septate hyphae and dichotomous branching, and cultures showed *A. fumigatus*. Treatment was initiated with oral voriconazole at 300 mg twice a day (b.i.d.) after a loading dose of 400 mg b.i.d. on the first day. The tacrolimus dose was reduced by 50%. Antifungal susceptibility testing using EUCAST methodology (6) showed that voriconazole was inactive (MIC > 16 μg/ml); MICs of itraconazole and posaconazole were 2 and 0.5 μg/ml, respectively. The amphotericin B MIC was 0.5 μg/ml. After the MIC results became available, voriconazole was replaced by posaconazole at 200 mg four times a day (q.i.d.), aiming at an exposure above 1 μg/ml. However, after 1 week of therapy under steady-state conditions, the trough plasma posaconazole concentration measured 0.6 μg/ml. The dosing regimen was changed to 200 mg six times daily with intake after the intake of high-fat-containing food. The increased posaconazole dose still yielded the same concentration after the second week of therapy.

In February, pus drained spontaneously from the operation wound. Upon presentation, our patient was severely septicemic. Nephrostomy catheter urine showed Gram-positive rods and cocci. The patient was started on piperacillin-tazobactam, caspofungin, and liposomal amphotericin B. Posaconazole treatment was discontinued. Ultrasonography showed pus surrounding the kidney transplant. Computed tomography showed that the infection had progressed to the lower pole of the transplant and abdominal wall. Although surgical drainage was performed, the patient died shortly afterwards.

A urine culture grew *Enterococcus faecalis* and *Corynebacterium* species. *A. fumigatus* was cultured from the double-J catheter. In addition to morphological identification, the iden-
Attenuated susceptibility of A. fumigatus to an azole drug has been suboptimal, as this signified total drug and not free exposure. The posaconazole trough level of 0.6 μg/ml (classification) was 0.5 (I) 0.5 (I) 5.1 5.9 6.5 7.1 18.4 5.8 4.1 1.1

<table>
<thead>
<tr>
<th>Site</th>
<th>Fungal culture result</th>
<th>MIC (μg/ml) (classification)</th>
<th>POS level (μg/g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abscess A. fumigatus</td>
<td>2 (I) &gt;16 (R) 0.5 (I)</td>
<td>5.1</td>
<td></td>
</tr>
<tr>
<td>Kidney (ewb) A. fumigatus</td>
<td>1 (S) &gt;16 (R) 0.5 (I)</td>
<td>5.9</td>
<td></td>
</tr>
<tr>
<td>Kidney (tissue) A. fumigatus</td>
<td>1 (S) &gt;16 (R) 0.5 (I)</td>
<td>6.5</td>
<td></td>
</tr>
<tr>
<td>Renal fat tissue A. fumigatus</td>
<td>1 (S) &gt;16 (R) 0.25 (S)</td>
<td>7.1</td>
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<tr>
<td>Liver</td>
<td>Negative</td>
<td>18.4</td>
<td></td>
</tr>
<tr>
<td>Spleen</td>
<td>Negative</td>
<td>5.8</td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>Negative</td>
<td>4.1</td>
<td></td>
</tr>
<tr>
<td>Blood</td>
<td>Negative</td>
<td>1.1</td>
<td></td>
</tr>
</tbody>
</table>

a ITZ, itraconazole; VCZ, voriconazole; POS, posaconazole; S, susceptible; I, intermediately susceptible; R, resistant.

b Classification according to recently proposed interpretative guidelines (12).

c In μg/ml (whole blood).

The efficacious area under the concentration-time curve (AUC) over the MIC for posaconazole is probably above 200, and conservative estimations are as high as 1,000 based on a nonneutropenic murine model of disseminated aspergillosis (4). The pharmacodynamic target of 200 could have been achieved with posaconazole plasma concentrations of 0.6 μg/ml if the infection had been caused by an A. fumigatus isolate with wild-type susceptibility. However, due to the elevated MICs, the AUC/MIC ratios for our patient were 30 to 60, at least 3.5- to 7-fold lower than the pharmacodynamic target. Plasma levels above 4 μg/ml would have been required to achieve a pharmacodynamic target of 200, which is impossible to achieve with the current formulation of posaconazole. Although the posaconazole tissue levels that we found in our patient exceeded 4 μg/ml, the calculation of the pharmacodynamic target is based on the plasma levels of the drug and not on tissue levels. Therefore, much higher tissue levels, i.e., those corresponding to a plasma level of 4 μg/ml, are probably required to achieve a high probability of treatment success.

Our case demonstrates that posaconazole should be used extremely cautiously for the treatment of patients with invasive aspergillosis caused by Aspergillus isolates with attenuated posaconazole susceptibility, due to unfavorable AUC/MIC ratios and a higher probability of treatment failure. Therapy with non-azole antifungal agents, e.g., lipid formulations of amphotericin B, may be an appropriate alternative treatment option when renal function is acceptable, although clinical experience with azole-resistant aspergillosis is still limited.

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REFERENCES


